High Incidence of Carcinosarcoma among Patients Previously Treated with Tamoxifen

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ABSTRACT: **Background:** Tamoxifen acts as an estrogen antagonist within the breast tissue. In the uterus, tamoxifen is an agonist for some estrogen receptors and can therefore cause hyperplasia or neoplasia in the endometrium.

Objectives: To compare characteristics of patients with uterine sarcoma who were and were not previously treated with tamoxifen.

Methods: The medical records of all women with uterine sarcoma who had been treated at the Carmel Medical Center in Haifa, Israel, during 2000–2013 were retrospectively reviewed. Disease characteristics, histological type of sarcoma, patient demographics, treatments and final outcomes were compared between patients who had and those who had not been exposed to tamoxifen.

Results: Of the 66 patients identified, 14 (21%) had been exposed to tamoxifen, one of them for 3 years and 13 for at least 5 years. Mean ages were 69 ± 8 and 66 ± 12 years for those exposed and those not exposed to the drug, respectively. Rates of uterine carcinosarcoma were 86% (12/14) and 44% (23/52), respectively ($P < 0.006$). Patients with carcinosarcoma were older than other sarcoma patients (73 ± 7 vs. 59 ± 11 $P < 0.005$).There were no statistically significant differences between the two groups in rates of diabetes mellitus, hypertension, dyslipidemia or heart disease. The mean time from diagnosis to death was 7.37 ± 0.42 years. The overall survival rates of carcinosarcoma patients were not statistically different from that of other sarcoma patients. Tamoxifen exposure was not associated with overall survival among all sarcoma patients, nor among the subgroup of carcinosarcoma patients.

Conclusions: Tamoxifen treatment was associated with elevated incidence of carcinosarcoma among women with uterine sarcoma, but was not found to be associated with prognosis or with co-morbidities.

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KEY WORDS: uterus, sarcoma, tamoxifen, carcinosarcoma, breast carcinoma

The uterus is the most common site of gynecological sarcomas. Nevertheless, uterine sarcomas are rare, accounting for approximately 1% of female genital tract malignancies and 3–7% of uterine cancers [1]. The aggressive behavior of uterine sarcomas is well recognized [2,3]; however, their rarity and histopathological diversity are reasons for the lack of consensus regarding risk factors and optimal treatment. Histologically, uterine sarcomas have been classified as carcinosarcomas (accounting for 40% of cases), leiomyosarcomas (40%), endometrial stromal sarcomas (10–15%), and undifferentiated sarcomas (5–10%) [4]. Leiomyosarcomas are derived solely from the myometrial compartment, and endometrial stromal sarcomas from the endometrial compartment. Carcinosarcoma, also known as malignant mixed mesodermal tumor or malignant mixed Mullerian tumor (MMMT), has sources in both compartments.

Carcinosarcoma, which shows both epithelial and stromal malignant differentiation, may arise from a common stem cell that produces epithelial tumors with a biphasic development. However, these neoplasms are currently classified as carcinomas since they are derived from a monoclonal neoplastic cell that shares more characteristics with epithelial than with stromal neoplasms. In addition, the epidemiology, risk factors and clinical behavior associated with carcinosarcoma suggest a closer relationship to endometrial carcinoma than to sarcoma [5].

Tamoxifen has been shown to be effective in improving survival for women with breast cancer and appears to decrease the risk of estrogen receptor-positive breast cancer in high risk populations of healthy women [6-9]. Tamoxifen has weak estrogenic properties that can produce endometrial cell proliferation and, consequently, increases the risk of endometrial cancer by as much as three- to sevenfold [6,7,10,11]. Since 2002, tamoxifen carries a Food and Drug Administration black box label that warns against the risk of uterine cancer [12]. A number of studies have indicated that the risk associated with this drug may be substantially higher for both carcinosarcoma and other uterine sarcomas [6,13].

In this study, we characterized the demographic, histopathologic, prognostic and clinical aspects of patients with uterine sarcomas and compared between those who were previously treated with tamoxifen and those who were not.

PATIENTS AND METHODS

We conducted a retrospective review of all patients diagnosed with uterine sarcomas from January 2000 to July 2013 at the Carmel Medical Center, Haifa, Israel. Patient data were collected from the hospital medical records, the electronic charting system (Clicks Medical Information System, Roshtov Software Ind., Omer, Israel), and the files of patients who were operated on by the hospital's gynecology-oncology staff. The study protocol was approved by the Ethical Review Committee of the Carmel Medical Center (Protocol number 021-37269). All histopathological diagnoses were performed and reviewed by the institution's senior pathologists.

Medical records were retrospectively reviewed and relevant clinical and pathologic data extracted, including age, parity, co-morbidities, time of diagnosis of breast cancer, duration of tamoxifen use, stage of sarcoma (according to the FIGO staging criteria 2009) [3], histological type of sarcoma, type of surgery, treatment, and the time of death. We analyzed the patient data according to two groups: women previously treated with tamoxifen and women who were not.

ANALYSIS

Statistical analysis was performed using SSPS software (SPSS Inc., version 15, Chicago, IL, USA). Student's *t*-test was used to test for statistical significance for continuous variables, and chi-square test for categorical variables. For comparison between more than two sets of variables we used the ANOVA model with logistic regression analysis. Kaplan-Meier survival curves were constructed for the groups defined by tamoxifen use and type of sarcoma. Patients were excluded at the date of death from another cause or at the end of May 2014.

RESULTS

We identified 66 patients who were diagnosed with uterine sarcoma during the study period, mean age 66 ± 12 years (range 41–89). Of those, 14 (21%) had been previously treated with tamoxifen due to a history of breast cancer. All but one of the patients (92%) used tamoxifen for at least 5 years, and one patient used it for only 3 years. The rest (n=52) were not exposed to tamoxifen and did not have breast cancer. Carcinosarcoma was diagnosed in 12 patients (85%) previously treated with tamoxifen and in 23 (44%) not exposed ($P < 0.006$) [Table 1]. The mean age at the diagnosis of sarcoma among patients previously exposed to tamoxifen was 69 ± 8 compared to 66 ± 12 years among those not exposed. The mean age of patients with carcinosarcoma was older than that of patients with other types of sarcomas (73 ± 7 vs. 59 ± 11, $P < 0.0001$).

There were no statistically significant differences between the two groups in the co-morbidities investigated (diabetes mellitus, hypertension, dyslipidemia, and heart disease) [Table 1].

Table 1. Clinical, treatment and prognostic characteristics of women with uterine sarcoma, according to exposure to tamoxifen

	Exposed to tamoxifen n=14 (%)	Not exposed to tamoxifen n=52 (%)	*P* value
Carcinosarcoma	12 (85%)	23 (44%)	< 0.006
Diabetes mellitus	4 (28%)	13 (25%)	NS
Hypertension	9 (64%)	34 (65%)	NS
Dyslipidemia	5 (34%)	26 (50%)	NS
Heart disease	4 (28%)	18 (34%)	NS
Adjuvant radiation	10 (71%)	26 (50%)	NS
Adjuvant chemotherapy	4 (28%)	22 (42%)	NS
Mean age, yr (mean ± SD)	69 ± 8	66 ± 12	NS
Overall 5 year survival	40%	45%	NS

NS = non-significant

The distribution of disease stages in the tamoxifen-exposed group was 36% diagnosed at stage IA and 30% at stage IB. In the group not exposed, 36% were diagnosed at stage IB, 15% at stage II, and 9% at stage IIIB. These differences did not reach statistical significance.

The mean time from the diagnosis of sarcoma to death or the end of follow-up was 7.37 ± 0.42 years. There was no significant difference in overall survival rates between those treated and those not treated with tamoxifen regarding all cases of uterine sarcoma ($P = 0.602$) [Figure 1A, Table 1], and regarding the subgroup of those with carcinosarcoma ($P = 0.957$) [Figure 1B]. In addition, overall survival did not differ between those with carcinosarcoma and those with other histological subtypes of sarcoma ($P = 0.698$) [Figure 1C].

DISCUSSION

In a cohort of women with uterine sarcomas, carcinosarcoma was more prevalent among those who had been exposed to tamoxifen than among those who had not, 85% vs. 44%. Carcinosarcoma occurs typically in post-menopausal women, and most often presents with abnormal vaginal bleeding and uterine enlargement. At presentation, extra-uterine spread (stages III–IV) is detected in up to one-third of cases. Up to 37% of patients with carcinosarcomas have a history of pelvic irradiation [14].

In 2009, the International Federation of Gynaecology and Obstetrics reclassified carcinosarcoma as a metaplastic endometrial carcinoma [3]. Findings that support this classification include association of carcinosarcomas with otherwise typical endometrial adenocarcinomas within the same hysterectomy specimen, the presence of pure adenocarcinoma in recurrences of carcinosarcomas, recurrence of apparently pure endometrial adenocarcinomas as carcinosarcomas, and a similar metastatic pattern of carcinosarcomas and endometrial adenocarcinomas

Figure 1 [A]. Overall survival of women with uterine sarcoma, according to treatment with tamoxifen

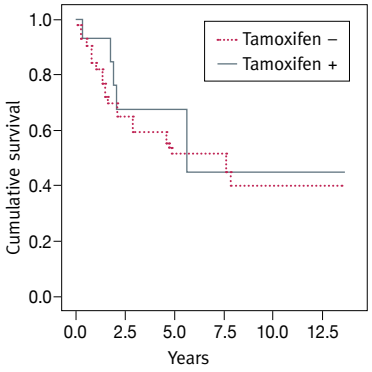


Figure 1 [B]. Overall survival of carcinosarcoma patients, according to treatment with tamoxifen

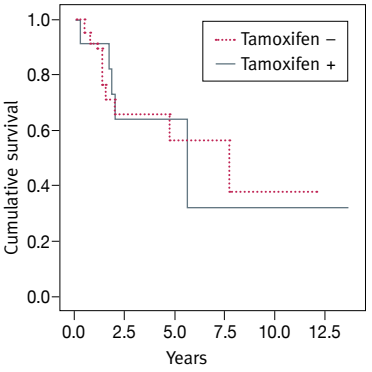
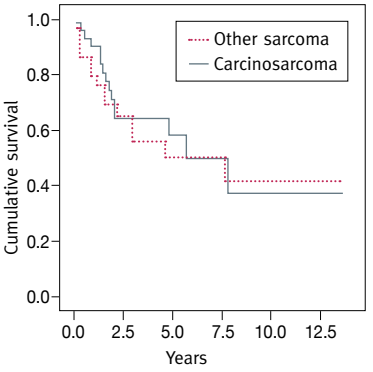


Figure 1 [C]. Overall survival of carcinosarcoma vs. other uterine sarcoma patients



[14]. A multicenter case-control study identified bodyweight, exogenous estrogen use, and nulliparity as risk factors for both carcinosarcoma and the more common endometrial carcinoma [15]. Furthermore, oral contraceptive use was found to be protective against the development of endometrial carcinomas – odds ratio (OR) 0.39, 95% confidence interval (95%CI) 0.26 – and carcinosarcoma (OR = 0.76, 95%CI = 0.25) [15].

More recently, a pooled analysis showed similar menstrual, hormonal and anthropometric risk factors for uterine sarcomas, including carcinosarcoma and endometrioid endometrial carcinomas [16]. However, median age at diagnosis was higher among women with carcinosarcoma than among those with other uterine sarcomas or endometrioid endometrial carcinomas. Likewise, our study showed an older mean age among women with carcinosarcoma than in those with other uterine sarcomas. Olah et al. [17] observed a bimodal age distribution among 423 cases of uterine sarcoma. They attributed this to a premenopausal peak of leiomyosarcoma and postmenopausal peak of carcinosarcoma. These findings suggest that, as with type 2 endometrial carcinoma, many patients with carcinosarcoma are postmenopausal, whereas those with leiomyosarcoma may be premenopausal or peri-menopausal at the time of diagnosis [17].

The association between endometrial carcinoma and tamoxifen is well established. Therefore, the elevated risk of carcinosarcoma among tamoxifen-treated women observed in our study and in others supports the classification of carcinosarcoma as endometrial carcinoma. For example, analysis of data from the Surveillance, Epidemiology, and End Results (SEER) of 39,451 breast cancer patients who had been treated with tamoxifen as first-line therapy for breast cancer revealed an increased overall risk of subsequent uterine corpus cancer by more than twofold compared to the general SEER population [4]. The relative risk was substantially greater for carcinosarcoma – observed to expected ratio (O/E) = 4.62, O = 34, 95%CI = 3.20 to 6.46 – than for endometrial adenocarcinomas (O/E = 2.07, O = 306, 95%CI = 1.85 to 2.32). Other retrospective studies in which tamoxifen was either an adjuvant therapy or its use was unspecified showed similar results [18-21].

In the current study, the observation that 13 of the 14 sarcoma patients (93%) who received tamoxifen did so for more than 5 years suggests a possible prolonged effect of the drug on uterine cells. Longer exposure to tamoxifen has been shown to be associated with greater risk for endometrial cancer and poorer prognosis [18].

In the current study, rates of diabetes mellitus, hypertension, dyslipidemia and history of heart disease were not significantly different between patients with and without exposure to tamoxifen. This suggests that exposure to tamoxifen may not affect these risk factors.

A possible explanation for the association of tamoxifen use with the risk for carcinosarcoma is based on a dual mechanism of action in the uterus [14]. As such, tamoxifen may initially be pro-estrogenic in the endometrium, giving rise to type 1 endometrioid carcinoma. However, after long-term use, it increases the incidence of type 2 uterine neoplasia such as carcinosarcoma, through a hormone-independent mechanism of action such as various types of growth factors [22].

Since all the women in the tamoxifen-exposed group had breast cancer and none of the women not exposed to tamoxifen had breast cancer, the current study was not able to exclude breast cancer as the risk factor for carcinosarcoma. However, a case-control study that comprised only breast cancer patients showed higher risk for endometrial carcinoma, more advanced disease and poorer prognosis among those treated with tamoxifen than those who were not [23], thus indicating that treatment with tamoxifen, not breast cancer, was the cause.

Although carcinosarcoma is associated with poor prognosis, and although our patients with carcinosarcoma were older, we did not find any difference in survival rates between women with carcinoma and women with other subtypes of sarcoma; nor did we find any differences in survival between patients with sarcomas (mainly carcinosarcomas) who were treated with tamoxifen

than those who were not. The mean time from diagnosis of the sarcoma to death or the end of follow-up was 7.37 ± 0.42 years. Our data contrast with a nationwide Dutch study that showed lower 3 year endometrial cancer-specific survival among tamoxifen users than non-users (76% for ≥ 5 years, 85% for 2–5 years, 94% for non-users, $P = 0.02$) [18]. Our 5 year overall survival rates of 40% and 45% for who were treated with tamoxifen and those who were not, respectively, were within the range reported by other studies of uterine sarcomas, 17–59% [2,3].

Interestingly, two case studies of patients with metastatic carcinosarcoma associated with tamoxifen documented more than 5 year disease-free survival [24,25]. Clara et al. [25] proposed that the development of carcinosarcomas in these patients was most likely related to the use of tamoxifen, yet the long-term survival could be related to their being carriers of *BRCA 1/2* mutations. The authors explained that *BRCA 1/2* mutations may enhance sensitivity to platinum chemotherapy drugs, at least in part due to the defect in the repair of DNA double-strand breaks integral to these mutations. In our study, we do not have information on the *BRCA* status; however, no differences in survival were observed among carcinosarcoma patients who took tamoxifen and those who did not.

The retrospective design is a limitation of this study, as is the small sample size and single-institution experience. Moreover, we cannot exclude the effect of breast cancer on survival. However, the rarity of sarcoma makes it difficult to investigate a large population of patients. An association linking uterine sarcomas in general and uterine carcinosarcoma, specifically, with the use of tamoxifen should be further evaluated molecularly and in a larger cohort of patients followed for survival data.

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"A man who lies to himself, and believes his own lies, becomes unable to recognize truth, either in himself or in anyone else, and he ends up losing respect for himself and for others"

Fyodor Dostoevsky (1821-1881), Russian novelist, journalist and philosopher. Dostoyevsky's literary works explore human psychology in the troubled political, social, and spiritual atmosphere of 19th century Russia. His major works are *Crime and Punishment*, *The Idiot*, *Demons*, and *The Brothers Karamazov*